Study of the k' or log k'–log P_{ow} correlation for a group of benzene derivatives and polycyclic aromatic hydrocarbons in micellar liquid chromatography with a C_8 column

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Abstract

The correlation between the capacity factor (k') or its logarithm (log k') and the logarithm of the octanol–water partition coefficient (log P_{ow}) for a group of 23 organic compounds (eleven benzene derivatives and twelve polycyclic aromatic hydrocarbons) was studied. The hydrophobicity range of the compounds chosen to study these correlations seems to be an important factor. In fact, the average r^2 values for 69 mobile phases of different composition and the 23-compound group is better for k'–log P_{ow} than for the log k'–log P_{ow} correlation. However, the average r^2 values for 84 different mobile phases proved to be better in the log k'–log P_{ow} correlation for the fifteen benzene and naphthalene derivatives group and similar in k'–log P_{ow} and log k'–log P_{ow} correlations for the ten monosubstituted benzene derivatives group.

1. Introduction

The hydrophobicity of an organic compound has been correlated with its biological activity or toxicity. The determination of the hydrophobicity has been used in various disciplines such as drug design and toxicology [1–3].

Traditionally, the logarithm of the octanol–water partition coefficient (log P_{ow}) has been used to measure the hydrophobicity of an organic compound. However, owing to the disadvantages of the standard "shake-flask" method for determining this partition coefficient [4], several attempts have been made in order to determine log P_{ow} by other techniques, some of

them chromatographic. A relationship between the logarithm of the capacity factor of a non-congeneric series of non-ionized solutes and their log P_{ow} values was obtained in reversed-phase high performance liquid chromatography (RP-HPLC) with aqueous–organic mobile phases [5].

As micelles are known as simple chemical models for biomembranes [6], micellar liquid chromatography (MLC), in which a surfactant at a concentration above its critical micellar concentration is used in the mobile phase, seems to be an interesting possibility for evaluating log P_{ow}.

Several studies on the correlation between MLC retention and log P_{ow} have been published [6–12]. However, some contradictory results have been obtained concerning which of the two

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parameters (k' or log k') best correlates with log P_{ow}.

In this work, the correlation between k' or log k' and log P_{ow} was studied for a group of 23 organic compounds (eleven benzene derivatives and twelve polycyclic aromatic hydrocarbons) in an MLC system. Sodium dodecyl sulphate (SDS) and hexadecyltrimethylammonium bromide (CTAB) were used as surfactants. These micellar phases were modified with methanol, n-propanol or n-butanol at different percentages.

2. Experimental

2.1. Apparatus

The chromatograph consisted of a Model 1050 pump, a Model 1050 automatic injector, a Model 1050 spectrophotometric detector of variable wavelength and an HP 3394 integrator (all from Hewlett–Packard).

Retention data for the fifteen benzene and naphthalene derivatives in the SDS and CTAB mobile phases in the absence and presence of n-propanol and n-butanol modifiers and for the 23 compounds in SDS–10% methanol were obtained with a Spherisorb C_8 column (15 cm × 4.0 mm I.D.) ($d_p = 5$ μm) (Teknokroma). In all mobile phases modified with alcohols, the concentration of the alcohol was 3, 5 or 10%.

Retention data for the eight polycyclic aromatic hydrocarbons in an MLC system (using SDS and CTAB mobile phases modified with n-propanol and n-butanol with a surfactant concentration ranging from 0.050 to 0.140 M) were also used in this study. Data on these mobile phases with a surfactant concentration ranging from 0.050 to 0.120 M were taken from Ref. [13].

A 0.45-μm filter and a filtration system (Millipore) were used.

2.2. Reagents

SDS, CTAB, methanol, n-propanol and n-butanol (all from Merck) were used as received.

Water purified with a Milli-Q system (Millipore) was used.

Benzene derivatives and polycyclic aromatic hydrocarbons were **1** = benzene, **2** = benzylic alcohol, **3** = benzamide; **4** = toluene, **5** = benzonitrile, **6** = nitrobenzene, **7** = phenol, **8** = 2-phenylethanol, **9** = chlorobenzene, **10** = phenylacetonitrile, **11** = 3,5-dimethylphenol, **12** = naphthalene, **13** = 1-naphthol, **14** = 2-naphthol, **15** = 1-naphthylamine, **16** = pyrene, **17** = phenanthrene, **18** = 2,3-benzofluorene, **19** = fluorene, **20** = fluoranthene, **21** = acenaphthylene, **22** = acenaphthene and **23** = anthracene.

2.3. Procedure

Micellar mobile phases were prepared by dissolving the appropriate amount of surfactant and alcohol in water in an ultrasonic bath followed by filtration. Stock solutions of test solutes were prepared in the mobile phase itself and their concentrations were adjusted to permit their detection from the injection of a 20-μl volume of sample. The void volume of the column for SDS micelles was determined from the retention time of the peak originating from the injection of the nitrate anion into the chromatographic system. For CTAB mobile phases, the first deviation of the baseline was employed.

The column and the mobile phase were water jacketed and thermostated at $25 \pm 1°C$ with a circulating water-bath.

3. Results and discussion

The capacity factors for the 23 compounds in an MLC system in which 69 different mobile phases of CTAB and SDS modified with methanol, n-propanol or n-butanol were used.

As the retention of the fifteen benzene and naphthalene derivatives (**1–15**) in the chromatographic system was less than that of the other polycyclic aromatic hydrocarbons (**16–23**), it was possible to determine the capacity factor for the fifteen referenced compounds in mobile phases not modified by alcohols. Therefore, capacity

factor data for these compounds were obtained for 84 different mobile phases.

With the retention data obtained, the correlation between k' or log k' with log P_{ow} was studied by using the log P_{ow} values grouped in Table 1.

The average r^2 values pertaining to each surfactant concentration in the mobile phase (five, six or seven different concentrations of surfactant for a given mobile phase) are given at Table 2. These r^2 values are given for both the k'–log P_{ow} and the log k'–log P_{ow} correlation and for the three groups of the compounds studied: all 23 compounds (**1–23**), the fifteen benzene and naphthalene derivatives (**1–15**) and the ten monosubstituted benzene derivatives (compounds **1–10**).

As can be seen at Table 2, k' always correlates better with log P_{ow} than log k' for the group of 23 compounds studied. In fact, for all mobile

Table 1
Log P_{ow} values for the 23 compounds studied

No.	Compounds	Log P_{ow}
1	Benzene	2.13[a]
2	Benzyl alcohol	1.10[a]
3	Benzamide	0.64[a]
4	Toluene	2.69[a]
5	Benzonitrile	1.56[a]
6	Nitrobenzene	1.85[a]
7	Phenol	1.46[a]
8	2-Phenylethanol	1.36[a]
9	Chlorobenzene	2.84[a]
10	Phenylacetonitrile	1.56[a]
11	3,5-Dimethylphenol	2.35[a]
12	Naphthalene	3.37[a]
13	1-Naphthol	2.98[a]
14	2-Naphthol	2.84[a]
15	Naphthylamine	2.22[a]
16	Pyrene	4.88[a]
17	Phenanthrene	4.46[a]
18	2,3-Benzofluorene	5.03[b]
19	Flourene	4.18[a]
20	Flouranthene	4.50[b]
21	Acenaphtylene	3.48[b]
22	Acenaphthene	3.82[b]
23	Anthracene	4.45[a]

[a] Values taken from Ref. [6].
[b] Values taken from Ref. [14].

phases employed, the average r^2 values is greater in the k'–log P_{ow} correlation than in the log k'–log P_{ow} correlation irrespective of the nature of the surfactant in the mobile phase. In general terms, the best results are obtained with a low percentage of alcohol in the mobile phase (3 or 5%). The worst value for r^2 corresponding to the k'–log P_{ow} correlation is obtained for the SDS–10% methanol mobile phases.

Concerning the influence of the surfactant concentration on the k'–log P_{ow} correlation, the r^2 values obtained for each surfactant concentration (values not shown) indicated that, in many cases, the k'–log P_{ow} correlation improves when the surfactant concentration in the mobile phase decreases, especially in the case of CTAB.

Table 2 also shows that for the fifteen benzene and naphthalene derivatives, k' correlates better with log P_{ow} than log k' only in the case of CTAB mobile phases. A better correlation is obtained for log k'–log P_{ow} when SDS is employed as a surfactant. However, for all mobile phases used except SDS–10% methanol, although the average r^2 value is greater in the log k'–log P_{ow} correlation (0.8854), it is not significantly different from that corresponding to k'–log P_{ow} correlation (0.8655). For this group of compounds, the addition of n-propanol and n-butanol at low percentages (3 or 5%) to CTAB mobile phases seems to improve the k'–log P_{ow} and log k'–log P_{ow} correlations. However, with SDS mobile phases, the best correlations are obtained in the absence of alcohols.

With the ten monosubstituted benzene derivatives, a similar result to that with the fifteen benzene and naphthalene derivatives is obtained. The k'–log P_{ow} correlation is better than the log k'–log P_{ow} correlation only when CTAB is employed as a surfactant. However, for SDS mobile phases, the average r^2 values are very similar for both correlations (k'–log P_{ow} and log k'–log P_{ow}) and this also occurs for the average r^2 values corresponding to all mobile phases. The group of ten benzene derivatives is characterized by a general increase in the average r^2 values, especially for log k'–log P_{ow} correlation. With regard to the presence of alcohols in mobile phase, the addition of these organic

Table 2
Average of r^2 values corresponding to five, six or seven concentrations of surfactant in each mobile phase

Mobile phase	k' (23)	Log k' (23)	k' (15)	Log k' (15)	k' (10)	Log k' (10)
CTAB[a]	–	–	0.9082	0.8779	0.9255	0.8802
CTAB–3% PrOH[a]	0.9571	0.8534	0.9598	0.9076	0.9692	0.9284
CTAB–5% PrOH[a]	0.9518	0.8453	0.9609	0.9072	0.9773	0.9406
CTAB–10% PrOH[a]	0.9275	0.8365	0.9038	0.8876	0.9786	0.9573
CTAB–3% BuOH[a]	0.9566	0.8600	0.9757	0.9237	0.9610	0.9528
CTAB–5% BuOH[a]	0.9286	0.8400	0.9299	0.9097	0.9765	0.9642
CTAB–10% BuOH[a]	0.9015	0.8189	0.8355	0.8458	0.9689	0.9450
$\bar{r}^2$ [d]	0.9372	0.8423	0.9248	0.8942	0.9653	0.9383
SDS[b]	–	–	0.8547	0.900	0.9160	0.9271
SDS–10% McOH[b]	0.8750	0.8644	0.5770	0.7765	0.9183	0.9260
SDS–3% PrOH[b]	0.9410	0.9305	0.8283	0.8775	0.9337	0.9274
SDS–5% PrOH[b]	0.9393	0.9156	0.7824	0.8689	0.9278	0.9506
SDS–10% PrOH[c]	0.9292	0.9197	0.7798	0.8726	0.9083	0.9422
SDS–3% BuOH[b]	0.9485	0.9091	0.8075	0.9067	0.9363	0.9430
SDS–5% BuOH[b]	0.9417	0.8899	0.7936	0.8691	0.9403	0.9494
SDS–10% BuOH[b]	0.9245	0.8423	0.7981	0.8421	0.9517	0.9392
$\bar{r}^2$ [e]	0.9374	0.9012	0.8063	0.8767	0.9256	0.9398
$\bar{r}^2$ [f]	0.9373	0.8717	0.8655	0.8854	0.9454	0.9390
$\bar{r}^2$ [g]	0.9061	0.8680	0.7212	0.8309	0.9318	0.9325

Mobile phase components: MeOH = methanol; PrOH = n-propanol; BuOH = n-butanol.
[a] Average of r^2 values corresponding to five concentrations of surfactant in each mobile phase.
[b] As above for six concentrations.
[c] As above for seven concentrations.
[d] Average of r^2 values corresponding to all CTAB mobile phases.
[e] Average of r^2 values corresponding to all SDS mobile phases except SDS–10% methanol.
[f] Average of r^2 values corresponding to all CTAB and SDS mobile phases studied except SDS–10% methanol.
[g] Average of r^2 values corresponding to all SDS and CTAB mobile phases studied.

modifiers to CTAB and SDS mobile phases generally improves the k'–log P_{ow} and log k'–log P_{ow} correlations.

The results obtained demonstrate the importance of the hydrophobicity range of compounds on the k' or log k'–log P_{ow} correlation. In fact, for all 23 compounds studied (hydrophobicity ranged from 0.64 to 5.03) k' correlated better with log P_{ow} than log k'. For the group of fifteen benzene and naphthalene derivatives (log P_{ow} ranged from 0.64 to 3.37) or the group of ten monosubstituted benzene derivatives (log P_{ow} ranged from 0.64 to 2.84) k' and log k' correlated similarly with log P_{ow} or even log k' correlated better with log P_{ow} than k', especially if SDS mobile phases were employed. These results are grouped in Fig. 1, showing the Box plot for average of r^2 values for the three groups of compounds studied and for k'–log P_{ow} and log
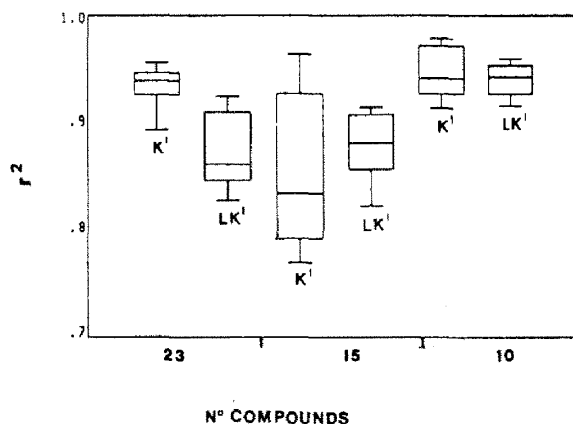

Fig. 1. Box plots for the average of r^2 values for three groups of compounds and for k'–log P_{ow} and log k'–log P_{ow} correlations. All mobile phases except SDS–10% methanol have been considered.

k'–log P_{ow} correlations. All mobile phases except SDS–10% methanol have been included in Fig. 1.

Figs. 2 and 3 show the variation of k' and log k' with log P_{ow} for CTAB and SDS mobile phases modified with 3% n-propanol and for concentrations of both surfactants of 0.05 and 0.120 M. The curvature observed for log k'–log P_{ow} plots can be explained by the solubility limit theory developed by Hinze and Weber [15]. For compounds with low log P_{ow} values, the solutes are as water soluble as they can be, so the water–stationary phase partitioning plays its largest role for these solutes. Highly hydrophobic solutes become insoluble in water, and then

the micelle-stationary phase equilibrium becomes predominant. In this equilibrium the two phases are chemically similar and the partition coefficient approaches unity and becomes independent of hydrophobicity. The log k'–log P_{ow} curve flattens.

The point on the curve where the "break" occurs is a value of log P_{ow} limit which can depend on the nature of the surfactant and/or the effect of alcohols. This explains why log k'–log P_{ow} correlation improves when the most hydrophobic compounds are eliminated on the curve (see Fig. 1).

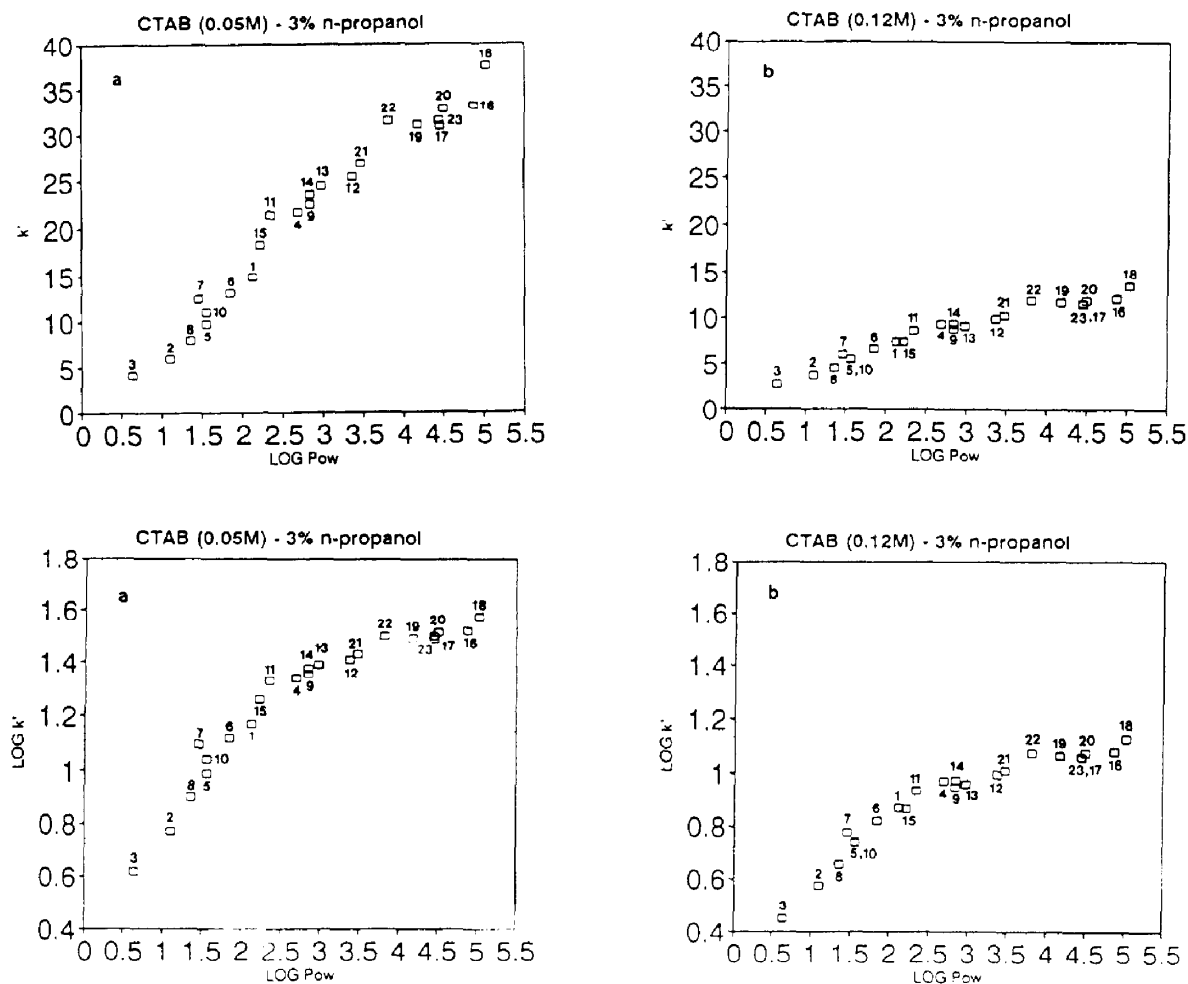Figs. 2 and 3 also show that a higher dispersion of experimental points occurs when SDS

Fig. 2. Variation of k' and log k' with log P_{ow} for a CTAB–3% n-propanol mobile phase: (a) 0.05 M CTAB; (b) 0.12 M CTAB.
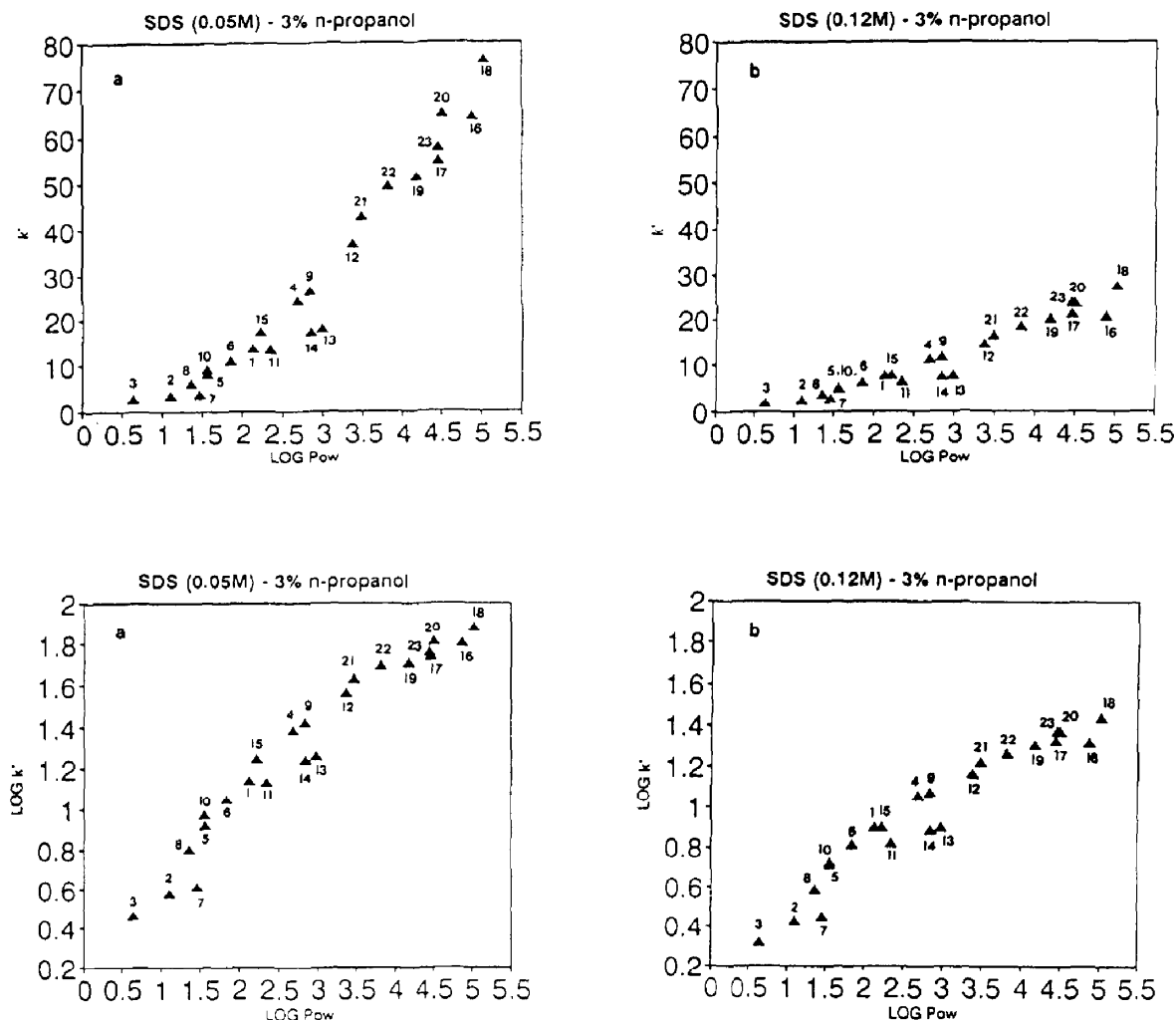
Fig. 3. Variation of k' and log k' with log P_{ow} for a SDS–3% n-propanol mobile phase: (a) 0.05 M SDS; (b) 0.12 M SDS.

mobile phases are used versus CTAB mobile phases.

A 0.050 M CTAB mobile phase modified with 3% n-propanol was chosen to calculate log P_{ow} from the experimental capacity factor data and the equation of the straight line. These calculated log P_{ow} values are plotted versus the experimental values in Fig. 4. The equation used to obtain these calculated log P_{ow} values was

$$k' = 0.2852 + 7.3770 \log P_{ow}$$

$$r^2 = 0.9615$$

and the average of the relative error obtained

between the calculated and experimental values was 9.56%.

4. Conclusions

From the results presented in this work and for the group of benzene derivatives and polycyclic aromatic hydrocarbons studied, the following conclusions can be drawn. For the 23 benzene derivatives and polycyclic aromatic hydrocarbons, k' always correlates better with log P_{ow} than log k', irrespective of the nature of the surfactant present in mobile phase and the na-
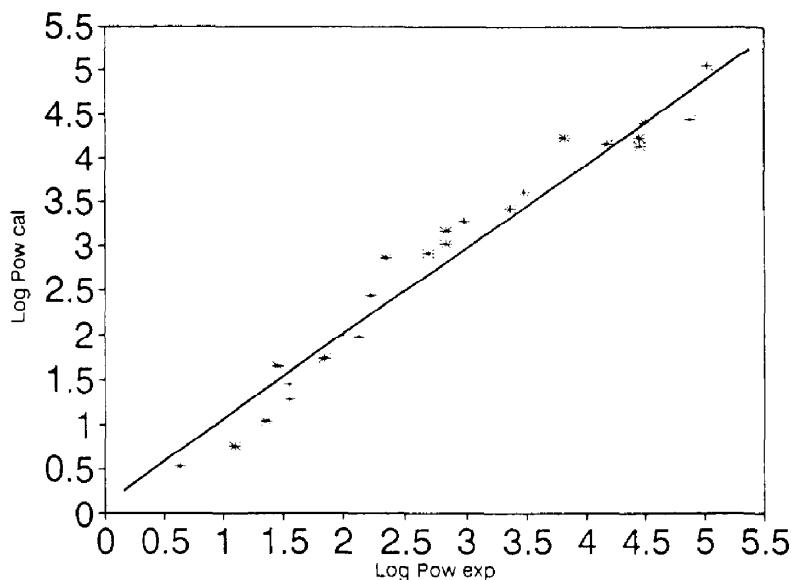
Fig. 4. Calculated versus experimental log P_{ow} values. The calculated values were obtained by means of the equation of the straight line corresponding to the variation of k' with log P_{ow} for a 0.05 M CTAB–3% n-propanol mobile phase.

ture and percentage of the alcohol used as modifier. However, for the fifteen benzene and naphthalene derivatives and the ten monosubstituted benzenes, k' correlates better with log P_{ow} than log k' only when CTAB mobile phases are used, the log k'–log P_{ow} correlation being similar to or even better than the k'–log P_{ow} correlation if SDS mobile phases are used. These results show that the hydrophobicity range of the compounds chosen is an important factor to be taken into account in this kind of study. Then, depending on the situation, either k' or log k' might better fit the data and one must therefore try both and use the one with the best correlation.

Acknowledgements

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